Administration Time–Dependent Effects of Aspirin in Women at Differing Risk for Preeclampsia

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Abstract—This study extends previous results on the effects of low-dose aspirin on blood pressure in pregnant women at differing risk of developing hypertension in pregnancy and who received aspirin at different times according to their rest-activity cycle. A double-blind, randomized, placebo-controlled trial was conducted in 240 pregnant women randomly assigned to 1 of 6 groups according to treatment (placebo or aspirin, 100 mg/d, starting at 12 to 16 weeks of gestation) and the time of treatment: on awakening (time 1), 8 hours after awakening (time 2), or before bedtime (time 3). Blood pressure and heart rate for each subject were automatically monitored for 2 days every 4 weeks from the day of recruitment until delivery, as well as at puerperium (6 to 8 weeks after delivery). Subjects were further divided for comparative purposes according to the results of the tolerance-hyperbaric test for early identification of those with a higher risk for developing hypertensive complications in pregnancy. Results indicated that there was no effect of aspirin on blood pressure at time 1 (compared with placebo). A blood pressure reduction was, however, highly statistically significant at time 2 and, to a greater extent, at time 3 (mean reductions of 14.2 and 9.6 mm Hg in 24-hour means for systolic and diastolic blood pressure, respectively, at the time of delivery compared with placebo given at the same time). Effects of aspirin on blood pressure were significantly larger for women with a positive test at the time of recruitment (P<0.001). Differences in blood pressure among pregnant women receiving aspirin at different times in the circadian cycle disappeared at puerperium (P>0.212). There was no effect of aspirin or placebo on heart rate. This study corroborates the statistically significant, time-dependent effect of low-dose aspirin on blood pressure in pregnant women with differing risk of developing hypertensive complications in pregnancy. Although the mechanism involved in the administration-time–dependent responsiveness of blood pressure to aspirin still remains uncertain, the use of doses of aspirin <80 mg/d that do not affect placental thromboxane, initiation of the use of aspirin after 16 weeks’ gestation, and the lack of circadian timing for aspirin administration could all explain the lack of positive results in previous clinical trials. (Hypertension. 1999;34;1016–1023.)

Key Words: aspirin ■ blood pressure ■ preeclampsia ■ hypertension, pregnancy ■ circadian rhythm

Several studies aimed to test the effects of low-dose acetylsalicylic acid (ASA, aspirin) in the prevention of preeclampsia have concluded that the beneficial effects of such treatment outweigh the adverse ones.1 These controlled trials were usually conducted in small groups of pregnant women selected according to several criteria for establishing a high risk of preeclampsia. The benefits shown by these small trials have not been corroborated by larger, randomized, controlled trials, usually carried out in the general obstetric population.2–4 These larger studies concluded that the use of low-dose ASA during pregnancy was safe for the fetus, the newborn, and the mother, but the results did not support the routine prophylactic use of ASA for the prevention of preeclampsia. Although the women in these larger trials were thought to be at increased risk for preeclampsia, it developed in <10% of the women investigated. This outcome may in fact have been due to the inclusion of many women at low risk for preeclampsia. A recent study involving only women at high risk concluded that, despite the absence of adverse effects, 60 mg/d ASA did not reduce the incidence of preeclampsia in women with pregestational insulin-treated diabetes mellitus, chronic hypertension, multifetal gestations, or a history of preeclampsia.5

Some relevant issues, not yet properly and fully addressed, still leave unresolved whether or not low-dose ASA is useful for prophylactic intervention in pregnancy.6 Regarding the most frequently used dose, results from a recent study suggest that doses of 50 to 60 mg/d of ASA are effective in inhibiting platelet thromboxane but may not be sufficient to inhibit placental thromboxane.7 A meta-analysis of low-dose ASA
for the prevention of IntraUterine Growth Retardation (the IUGR Study) further indicated that the preventive effect was greater at higher doses (100 to 150 mg/d) compared with lower doses (50 to 80 mg/d). Regarding duration of treatment, most clinical trials published so far included women at up to 28 or even 32 weeks of gestation at the time of entry into the study. A recent retrospective study on patients who received 100 mg/d ASA concluded that success (no pre-eclampsia) was associated with ASA starting before 17 weeks of gestation. A statistically significant reduction in IUGR and perinatal mortality was also found among women included before the 17th week of gestation compared with women who entered later in a meta-analysis that included >13 000 pregnant women. Moreover, differing predictable patterns of maternal blood pressure (BP) variability during gestation have been identified for healthy and complicated pregnancies. In clinically healthy pregnant women, BP steadily decreases up to the middle of gestation and then increases up to the day of delivery, with final BP values similar to those found early in pregnancy in the same women. Women who develop hypertensive complications in pregnancy are characterized, however, by a stable BP until the middle of gestation and by a continuous, linear increase of BP with gestational age throughout the second half of pregnancy. These differing patterns of BP variation already provide a highly statistically significant difference of 13 mm Hg in systolic BP (SBP) between healthy and complicated pregnancies by the end of the first trimester of pregnancy. These results suggest that any prophylactic effect in pregnancy should be studied by including women who start using ASA very early, i.e., not later than 17 weeks of gestation. Finally, the time of ASA administration could also be relevant. An administration time-dependent effect of low-dose ASA on BP in pregnant women has been recently documented in clinically healthy volunteers as well as in patients with mild hypertension. Moreover, results from a previous double-blind, randomized, controlled clinical trial on the influence of low-dose ASA on BP in pregnant women indicated a highly statistically significant (P < 0.001) administration time-dependent effect on BP by ASA. There was no effect of ASA on BP when administered on awakening (compared with placebo), but the BP reduction was highly statistically significant when ASA was administered 8 hours after awakening and, to a greater extent, when administered at bedtime. No other study, published either before or after this one, reported whether the time of medication was under control and if so, at what time of day ASA was given to the pregnant women.

The need to identify those women destined to have hypertensive complications in pregnancy is also clear. Along these lines, the approach of establishing a time-specified tolerance limit reflecting the circadian variability in BP as a function of gestational age and then determining the hyperbaric index (area of BP excess above the upper limit of the tolerance interval) by comparison of any patient’s BP profile (obtained by ambulatory BP monitoring, or ABPM) with those intervals, the so-called tolerance-hyperbaric test (THT) has been shown to provide high sensitivity and specificity for the very early identification of subsequent hypertension in pregnancy. Accordingly, because BP measurement is the basis not only for the THT but also for diagnosing hypertension in pregnancy, we now report results from a clinical trial designed to study any possible time-dependent influence of ASA on BP in pregnant women with differing responses to the THT at the time of recruitment, who entered the study protocol at <17 weeks of gestation, and who were randomized to receive placebo or ASA (100 mg/d, a low dose, that one assumes will affect both maternal as well as placental thromboxane). Results were also extended by comparing the BP profiles obtained for the same women at puerperium, i.e., 6 to 8 weeks after delivery, which marked the termination of treatment with either ASA or placebo.

Methods

Subjects

We report data on 240 pregnant, white women (141 primipara) who fulfilled all required criteria for this trial (see below), who were at a higher risk for gestational hypertension or preclampsia than the general obstetric population, and who were thus receiving medical care at the Obstetric Physiopathology Service (high-risk unit) of the Hospital General Clínico Universitario de Galicia, Santiago de Compostela, Spain. Reasons for receiving medical care at this unit include, among others, family or personal history of either gestational hypertension, preclampsia, or chronic hypertension; cardiovascular, endocrine, bleeding, or metabolic disease; a personal history of spontaneous abortion; and multiple pregnancy, obesity, and adolescent or middle-aged nulliparous pregnancy (<18 or >35 years). The relative risk of gestational hypertension and preeclampsia in this unit is ~3.5 times that of the general obstetric population in our setting. Additional inclusion criteria for this trial were the absence of any condition requiring the use of antihypertensive medication, maternal age (18 to 40 years), and gestational age (<16 weeks). Exclusion criteria were, among others, multiple pregnancy, chronic hypertension, chronic liver disease, any disease requiring the use of anti-inflammatory medication, diabetes, and any other endocrine disease such as hyperthyroidism, as well as intolerance to the use of ABPM. Apart from the 240 women providing all required information, 10 subjects who provided <4 profiles of ABPM (4 spontaneous abortions and 6 who withdrew from the trial) were eliminated from the study. Another 5 subjects who missed >6 tablets during any given month were also eliminated; this restriction ensures the use of at least 80% of the medication every month and avoids inclusion of subjects who may have missed medication for at least a week anytime during pregnancy. The minimum sample size for this trial (96 women with either positive or negative THT for the total 6 treatment groups; see below) was set a priori with the objective to show, as statistically significant at the 95% level, a BP difference between ASA and placebo of ≥6 mm Hg in the 24-hour mean of BP at the time of delivery. The percentage of women with a positive THT in our setting is 39%. Therefore, the minimum sample size for groups of women with a positive THT result was obtained by including 2.5 times more the required number per group.

BP Assessment

The SBP, diastolic BP (DBP), and heart rate (HR) of each of the 240 women who completed the trial were automatically monitored every 30 minutes during the day (9 AM to 10 PM) and hourly during the night for 48 hours with a previously validated ABPM-630 Colin (San Antonio, Tex) device at the time of recruitment and then every 4 weeks until delivery. Additionally, BP and HR were also monitored according to the same sampling scheme at puerperium, ie, 6 to 8 weeks after delivery. BP series were eliminated from analysis when they showed an irregular schedule during the days of sampling, an odd sampling with spans of >3 hours without BP measurement, or a night resting span <6 or >12 hours. The total number of BP series provided by the women under investigation fulfilling all
mentioned requirements set a priori was 1844. During BP sampling, all women were following their usual diurnal waking (~8 AM to approximately midnight) and nocturnal resting routine and, following their normal daily activity routine with minimal restrictions: they were instructed to follow a similar schedule during the 2 days of BP sampling and to avoid the use of medication (including ASA) for the duration of the trial. ABPM was performed in addition to the woman’s routine antenatal care, and no woman was hospitalized during monitoring. The BP cuff was worn on the nondominant arm. Cuff size was determined by upper arm circumference at the time of each visit. ABPM always started between 10 AM and 1 PM. During monitoring, each subject maintained a diary regarding information about her activity cycle, dietary consumption, physical activity, emotional state, and other external or internal stimuli possibly affecting BP.

Medications

The volunteers were randomly assigned (double-blind, randomized, placebo-controlled trial) at the time of their first visit to the hospital to 1 of 6 groups, defined according to treatment (placebo, 116 subjects; or ASA 100 mg/d, 124 subjects) and to the timing of daily administration of ASA and placebo: on awakening (time 1: 38 on placebo, 38 on ASA), 8 hours after awakening (time 2: 39 on placebo, 41 on ASA), or before bedtime (time 3: 39 on placebo, 45 on ASA). Baseline characteristics related to age, weight, height, and 24-hour mean BP values obtained from the first profile of ABPM (sampled before treatment started) were similar for all 6 groups of treatment, whether positive-THT, negative-THT, or all subjects combined were considered. Oral ingestion of ASA or placebo started at 12 to 16 weeks of gestation and continued until the day of delivery. The dose of 100 mg used in this trial corresponds to the actual lower dose commercially available in Spain. The median numbers of tablets taken by the women investigated were 169 in the ASA groups and 164 in the placebo groups. Compliance was measured on the basis of tablet count at the time of each visit. Placebo (microcrystalline cellulose, corn starch, saccharin, and citric acid [included to simulate the flavor of ASA]) and ASA (100-mg uncoated tablets) were prepared in identical presentation and provided monthly to the volunteers in a box containing 3 blister packs, each with 10 tablets. The boxes, grouped in packs of 7 (to cover medication for the duration of pregnancy) and labeled with the randomization number, were assigned to each patient at the time of her recruitment. The State Ethical Committee of Clinical Research as well as the Spanish Health Minister approved the study. All volunteers signed consent forms before entering the study.

Statistical Methods

Original oscillometric data from each of the 1844 BP series were edited according to commonly used criteria for the removal of outliers and measurement errors. The remaining data were first analyzed by the use of CHRONLAB, a software package for biological signal processing by linear and nonlinear least-squares estimation that, among other methods, includes single and population multiple-components analysis. In particular, each BP series was analyzed by least-squares fit of a multiple-component curve with periods of 24 and 12 hours to determine the rhythm-adjusted mean, or MESOR (midline estimating statistic of rhythm; average value of rhythmic function fitted to the data) and the amplitudes of both components. This model has been shown to describe sufficiently well the circadian pattern of BP variability, despite the fact that other ultradian rhythms can be demonstrated as statistically significant in some but not all individuals studied by 48-hour ABPM. Because the data were obtained at an nonequidistant sampling rate covering 2 cycles (48 hours), the MESOR provides a more accurate estimation of the true 24-hour mean than does the average of all BP values, which usually overestimate the true mean due to denser sampling during activity. The estimates of the 24-hour mean thus normalized were used to establish their pattern of variation for the duration of treatment for each of the 6 groups of pregnant women with either a positive or negative THT result by polynomial regression analysis. Effects of medication (placebo or ASA) and circadian time of treatment on BP during duration of treatment, as well as at puerperium, were evaluated by ANOVA.

Results

Placebo Administered at Different Times of the Day

Figure 1 shows the variation in the 24-hour mean (expressed as a percent of the value obtained for each subject before treatment started) of SBP (top) and DBP (bottom) during gestation (expressed in months from the pretreatment monitoring) in pregnant women with a negative (left) or positive (right) THT who were receiving placebo at different circadian times, starting at 12 to 16 weeks of pregnancy. This figure presents the histograms with the average values for 24-hour mean BP with their SEM for each month of treatment during gestation; second, the figure also shows the best model of predictable BP variability during gestation for each group of women obtained by polynomial regression analysis. Results in Figure 1 indicate that, for all groups of pregnant women with a negative THT result at the time of recruitment (and thus, with a lower risk for preeclampsia compared with women with a positive test result) who received placebo, BP followed a predictable pattern of variation that can be approximated by a second-order model in time (months of treatment). Figure 1 also shows nonsignificant changes in SBP and DBP until the 20th week of pregnancy (~1.5 months of treatment), followed by an increase in BP until the day of delivery (~6.5 after treatment started). This pattern of variation is fully equivalent to that previously shown for the BP of clinically healthy, pregnant women sampled on several occasions during their gestation but who were receiving no treatment. For women with a positive THT result at the time of entry, Figure 1 (right) indicates a linear increase in BP up to the time of delivery, equivalent to the pattern previously described for women who developed gestational hypertension or preeclampsia sampled on several occasions during their pregnancy and who received no treatment. Ninety-two percent of all women with a positive THT result included in Figure 1 actually developed hypertensive complications in their pregnancy. Figure 1 also indicates that the model of variation for the 24-hour mean BP during gestation was similar for all 3 groups of pregnant women receiving placebo within each class defined according to the THT. There was no statistically significant difference among groups of women in the average value of 24-hour mean BP or HR (not shown) at any time during gestation (P>0.192 in all cases).

ASA Administered at Different Times of the Day

Figure 2, on the left, compares the predictable variation in BP during time of treatment in pregnant women with a negative THT result who were receiving 100 mg/d of ASA at different times of the day. This predictable pattern again followed a
second-order model for both SBP and DBP in all groups of women. In opposition to the results shown in Figure 1 for pregnant women receiving placebo, the models of BP variation during gestation obtained for women with a negative THT and receiving ASA at different circadian times were not similar ($P<0.001$ in a test for comparison of second-order coefficients from the regression models for both SBP and DBP). Results from Figure 2 indicate a highly statistically significant time-dependent effect of low-dose ASA on BP. There was no effect when ASA, compared with placebo, was administered on awakening; the BP reduction, however, was statistically significant when ASA was taken 8 hours after awakening, and, to a greater extent, when ASA administered before bedtime. Results from ANOVA indicate that the differences between treatment groups in the mean values of BP were statistically significant as soon as the first month of treatment for SBP ($P<0.001$) and DBP ($P=0.006$). Results further indicate that, at the time of delivery, the use of 100 mg/d of ASA before bedtime decreased BP on an average of 10.6 mm Hg (SBP) and 7.7 mm Hg (DBP) compared with use of the same dose of ASA on awakening.

Figure 2 right, also shows that BP in women with a positive THT result who were receiving ASA on awakening followed a linear increase with gestational age. Women receiving ASA 8 hours after awakening or before bedtime, however, were characterized by BP changes during gestation that were similar to those obtained from women with uncomplicated pregnancies. The administration time–dependent effects of ASA on BP indicate that, at the time of delivery, there was an estimated difference of 16.1 mm Hg in the 24-hour mean SBP and of 9.8 mm Hg in DBP between women receiving ASA on awakening compared with those receiving the same medication and dose thereof before bedtime. The differences between ASA given at time 2 and at time 3 were also statistically significant: there was an additional reduction of 9.3 mm Hg in SBP and of 5.5 mm Hg in DBP when ASA was ingested at the most convenient time (bedtime) for practical reasons. Comparison of the histograms represented in Figure 2 also indicates that the administration time–dependent effects of ASA were statistically larger for women with a positive THT result at the time of entry compared with those women with a negative test result especially when ASA was taken at bedtime ($P<0.001$). Despite the time-dependent effects of ASA on BP as documented in Figure 2, there was no statistically significant effect of ASA on HR (always $P>0.242$; not shown).

**Placebo Versus ASA Administered at Different Circadian Times**

Comparison of the histograms represented in Figures 1 and 2 for women receiving either ASA or placebo on awakening indicates that the model for the variation in 24-hour mean BP during gestation was similar for both groups of pregnant women. Moreover, there was no statistically significant difference among groups of women in the average value of the 24-hour mean BP at any time during gestation ($P>0.174$ in all cases). At the time of delivery, the predictable average difference in 24-hour mean BP between women receiving placebo and those receiving ASA on awakening was not statistically significant ($P=0.229$ for SBP and 0.144 for DBP in women with a negative THT; $P=0.488$ for SBP and 0.597 for DBP in women with a positive THT).
A further comparison of the histograms represented in Figures 1 and 2 indicates that the models obtained for women receiving placebo versus ASA 8 hours after awakening were not similar ($P<0.001$ in a test for comparison of second-order coefficients from the regression models for both SBP and DBP). Results indicate that the differences in the average value of the 24-hour mean BP between women receiving placebo versus ASA at time 2 were already statistically significant after the first month of treatment ($P=0.021$). At the time of delivery, the statistically significant difference ($P<0.001$) in the mean value of BP between women receiving placebo and those receiving ASA at time 2 was 8.1 mm Hg for SBP and 5.3 mm Hg for DBP for women with a negative THT result (6.3 and 4.1 mm Hg for SBP and DBP, respectively, for women with a positive test result).

Figures 1 and 2 also summarize the effects on 24-hour mean SBP (top) and DBP (bottom) of a daily dose of either placebo or 100 mg of ASA ingested at bedtime in pregnant women at high risk for preeclampsia. When the pregnant women took ASA, BP continued to decrease slightly after the second month of treatment, without reaching the mean BP level obtained before treatment started. Results indicated statistically significant differences in BP between placebo and ASA given at bedtime after the first month of treatment ($P<0.001$). Moreover, at the time of delivery, there was a predictable BP reduction of 13.1 mm Hg in the 24-hour mean SBP and of 8.0 mm Hg in the 24-hour mean DBP for those women with a negative THT result who were receiving 100 mg/d of ASA at bedtime compared with the women receiving placebo at the same circadian time. The reduction was 15.9 mm Hg for SBP and 10.9 mm Hg for DBP for women with a positive THT result at the time of recruitment and, thus, who had an even higher risk for preeclampsia than those women with a negative test.

**Effects of ASA and Placebo on BP at Puerperium**

Comparison of the histograms presented in Figure 3 (left) for all women (irrespective of results from the THT) receiving placebo at different circadian times indicated no differences among the 3 groups of subjects with respect to SBP and DBP). Results indicate that the differences in the average value of the 24-hour mean BP between women receiving placebo versus ASA at time 2 were already statistically significant after the first month of treatment ($P=0.021$). At the time of delivery, the statistically significant difference ($P<0.001$) in the mean value of BP between women receiving placebo and those receiving ASA at time 2 was 8.1 mm Hg for SBP and 5.3 mm Hg for DBP for women with a negative THT result (6.3 and 4.1 mm Hg for SBP and DBP, respectively, for women with a positive test result).

Figures 1 and 2 also summarize the effects on 24-hour mean SBP (top) and DBP (bottom) of a daily dose of either placebo or 100 mg of ASA ingested at bedtime in pregnant women at high risk for preeclampsia. When the pregnant women took ASA, BP continued to decrease slightly after the second month of treatment, without reaching the mean BP level obtained before treatment started. Results indicated statistically significant differences in BP between placebo and ASA given at bedtime after the first month of treatment ($P<0.001$). Moreover, at the time of delivery, there was a predictable BP reduction of 13.1 mm Hg in the 24-hour mean SBP and of 8.0 mm Hg in the 24-hour mean DBP for those women with a negative THT result who were receiving 100 mg/d of ASA at bedtime compared with the women receiving placebo at the same circadian time. The reduction was 15.9 mm Hg for SBP and 10.9 mm Hg for DBP for women with a positive THT result at the time of recruitment and, thus, who had an even higher risk for preeclampsia than those women with a negative test.

**Discussion**

The major conclusion from this study, corroborating previous results obtained from a much smaller number of subjects, is
that ASA selectively decreases BP as a function of the time of its administration in relation to the rest-activity cycle of each individual pregnant woman. Results indicate that (1) there is no statistically significant difference in BP ($P > 0.192$) between women receiving placebo at different circadian times; (2) there is a highly statistically significant BP reduction that is consistently increased during gestation in women receiving 100 mg/d of ASA ($P < 0.001$ from a comparison of ASA versus placebo but without taking into account circadian time of medication); and (3) the effect of ASA on BP is markedly dependent on the time of its administration: there is no effect when ASA is taken on awakening, but the BP reduction is highly statistically significant when ASA is ingested 8 hours after awakening and, to a larger extent, before bedtime (Figure 2). Moreover, the effects of ASA, ingested before bedtime, on BP were statistically larger in women with a positive THT result at the time of recruitment. Despite the highly statistically significant time-dependent effect of ASA on BP, there was no effect on HR. Finally, Figure 3 shows that at puerperium, ie, 6 to 8 weeks after discontinuation of treatment, there was no statistically significant difference in 24-hour mean SBP or DBP among the groups of women who received ASA or placebo during most of their pregnancies.

The sample size of this trial, obtained a priori with the objective of corroborating any possible differing effect of low-dose ASA on BP compared with placebo in women with differing response to the THT during the first trimester of pregnancy is, however, still half that necessary to derive conclusions regarding a possible reduction in the incidence of hypertensive complications by the use of low-dose ASA. With this limitation notwithstanding, a brief summary of outcomes in the women investigated could be of interest. The number of documented cases of IUGR was higher for placebo (14 cases) compared with ASA (6 cases). Preterm delivery (before 37 weeks of gestation) was 6 times higher among women receiving placebo (13 cases). The number of pregnancies complicated with gestational hypertension (conventional BP values $>140/90$ mm Hg for SBP/DBP without a clinical record of hypertension before pregnancy) and preeclampsia (here defined as gestational hypertension and proteinuria $>300$ mg/24 h, with or without edema) was higher among women receiving placebo; the difference in incidence of these 2 complications between placebo and ASA is, despite limitations in sample size, already statistically significant ($P = 0.009$). The differences are larger and highly statistically significant ($P = 0.003$) if we compare the incidence of hypertension for the groups of placebo and ASA taken at time 1 (when there was no effect on BP) with the incidence in women receiving ASA at times 2 and 3 (when ASA actually reduced BP compared with placebo). Moreover, there was no difference in the incidence of gestational hypertension and preeclampsia when we compared placebo with ASA at time 1 ($P = 0.368$). The number of cases with bleeding in the third trimester was 5 on placebo and 2 on ASA. Except for 1 documented case of placental abruption (a woman taking ASA at time 1), there was no other complication documented in the women under investigation. Therefore, even though the sample size was still too small to draw more definitive conclusions, the use of low-dose ASA was not associated with an increase in maternal or neonatal complications; low-dose ASA was safe for the mother, the fetus, and the newborn. Finally, a statistically significant
decrease of 59% in the number of documented cases of gestational hypertension and preeclampsia was observed when ASA was administered at times 2 and 3. It is also important to point out that, among women with a positive THT result at the time of recruitment and who were receiving medication before bedtime, all subjects receiving placebo in contrast to only 20% of those receiving ASA actually developed either gestational hypertension or preeclampsia.

With respect to the administration time-dependent BP lowering by ASA compared with placebo, recent studies have also shown statistically significant circadian rhythms in thromboxane and prostacyclin production, circulating platelets, platelet aggregation, clotting and fibrinolytic inhibitors, circulating angiotensin II, angiotensin sensitivity in pregnancy, and the inhibition of platelet aggregation produced by ASA. Another factor to be taken into consideration is the pharmacokinetic observation that ASA exhibits a faster drug-disappearance rate when administered during the morning compared with the evening. These results complement the time-dependent changes that have been described when the pharmacokinetics of nonsteroidal anti-inflammatory drugs were investigated in humans.

In summary, the results indicate a statistically significant, time-dependent effect of low-dose ASA on BP in pregnant women at high risk of developing gestational hypertension or preeclampsia. The mechanism(s) involved in the responsiveness of BP to ASA administered at different times according to the rest-activity cycle is unknown and awaits further investigation. The hypothesis that a time-dependent effect of ASA on thromboxane production could also be at least partly responsible for the time-dependent effects of ASA on BP and on the reduction in the incidence of gestational hypertension and preeclampsia gains relevance given the lack of any effect of ASA on HR. On the other hand, ASA has also been shown not only to restore vascular refactoriness to angiotensin II in women at risk for preeclampsia but also to produce a dose-dependent BP reduction and >30% inhibition of angiotensin II. We may at least conclude that any prospective study on the prophylactic advantages of ASA should systematically investigate the effect of timing. These results should be taken into account in the optimization of long-term ASA administration at low dose for prevention of preeclampsia. Moreover, a new high-sensitivity test for the early identification of pregnant women who will subsequently develop gestational hypertension and preeclampsia, provides a useful tool for the identification of those women who will benefit most from the timed, prophylactic use of low-dose ASA in pregnancy. The use of ASA in doses <80 mg/d that do not affect placental thromboxane, initiation of the use of ASA after 16 weeks of gestation when differences in BP between healthy and complicated pregnancies are already highly statistically significant, and the lack of circadian timing for ASA administration (following the results from Figure 2 that corroborates and extends previous conclusions) could all explain the lack of positive results in previous clinical trials for the prevention of preeclampsia and its complications by the use of ASA.

Acknowledgments

This research was supported in part by grants from Conselleria de Educacion e Ordenacion Universitaria, Xunta de Galicia (XUGA-32202-B97); Direccio General de Enseñanza Superior, DGES (PM98-0106); and Vicerrectorado de Investigacion, Universidad de Vigo. Medication has been provided by Quimica Farmaceutica Bayer S.A.

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Hypertension. 1999;34:1016-1023
doi: 10.1161/01.HYP.34.4.1016

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